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Identification of novel bivalent mimetics of annonaceous acetogenins via a scaffold-hopping strategy

Yanghan Liu [a], Yongqiang Liu [b], Zhen Li [c], Guang-Biao Zhou [b], Zhu-Jun Yao [d,*], Sheng Jiang [a,*]

[a] Laboratory of Medicinal Chemistry, Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou 510530, China
[b] Division of Molecular Carcinogenesis and Targeted Therapy for Cancer, State Key Laboratory of Biomembrane and Membrane Biotechnology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China
[c] Department of Translational Imaging, The Houston Methodist Research Institute, Houston, TX 77030, United States
[d] State Key Laboratory of Coordination Chemistry, Nanjing National Laboratory of Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, 22 Hankou Road, Nanjing 210093, China

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ABSTRACT

A series of novel bivalent mimetics of annonaceous acetogenins have been designed, synthesized, and evaluated. Among these, compound **7** bearing a homopiperazine ring in the middle region exhibited more potent growth inhibitory activity and higher selectivity against cancer cells over normal cells by comparison with AA005. This work indicates that modification of the middle piperazine ring is a useful optimizing tool for the simplified acetogenin mimetics.

Annonaceous acetogenins are a class of natural polyketides isolated from Annonaceous plants, and more than 400 members have been found and characterized in the past three decades.[1–3] They were found to show a broad range of biological activities, such as anticancer, antimalarial, anthelmintic, antiviral, and antimicrobial effects. It is generally accepted that annonaceous acetogenins serve as the blockers of complex **I** (NADH-ubiquinone oxidoreductase) in mitochondria and reduce the production of ATP.[4,5] Annonaceous acetogenins have been attracting worldwide attention for a long period because of their unique chemical structures and attractive biological activities especially for their anticancer activities.[1,2,6] During our efforts of simplifying natural annonaceous acetogenins into the corresponding mimetics,[7–15] we successfully invented a simple analogue AA005 by replacement of the bis-THF rings of natural bullatacin with an linear ethylene glycol ether functionality. AA005 exhibited significant potency of inhibiting the proliferation of several human cancer cell lines and selective action between human cancerous and healthy cells.[8–10] Subsequently, we further developed an improved mimicking compound having a biphenyl moiety in the left hydrocarbon chain, showing more potent inhibitory activity against cancer cell proliferation and higher cell selectivity.[16]

Discovery of bivalent ligand inhibitors has proven to be a useful protocol in medicinal chemistry and gained worldwide attention due to the potential high functional affinities through bivalent ligand–receptor interactions.[17] We recently applied this concept into synthesizing a new series of linear dimeric analogues mimicking natural annonaceous acetogenins.[18] Unfortunately, these simpler dimers were identified to exhibit 8–100 times less potency than AA005 against the growth of SGC7901 cells. In this study, we want to report a new series of bivalent analogues by a scaffold-hopping strategy, which have simple structures and potent growth inhibitory activity.

As shown in Figure 1, the newly designed mimetics are composed of three functionalities: diverse analogues of ubiquinone at the terminal(s) (P), hydrophilic piperazine ring in the middle and hydrophobic hydrocarbon chain(s) as the linkers. The common γ-lactone moiety in the natural acetogenins is suggested to be essential for binding at the quinone binding site of mitochondria complex **I**. Previously, several groups including us found that replacement of the γ-lactone moiety of natural acetogenins with the quinone portion of ubiquinone could maintain or increase the potency of complex **I** inhibition.[18–21] These results indicated that the quinone portion of ubiquinone is a good functional

* Corresponding authors. Fax: +86 20 32015318 (S.J.).
E-mail addresses: yaoz@nju.edu.cn (Z.-J. Yao), jiang_sheng@gibh.ac.cn (S. Jiang).

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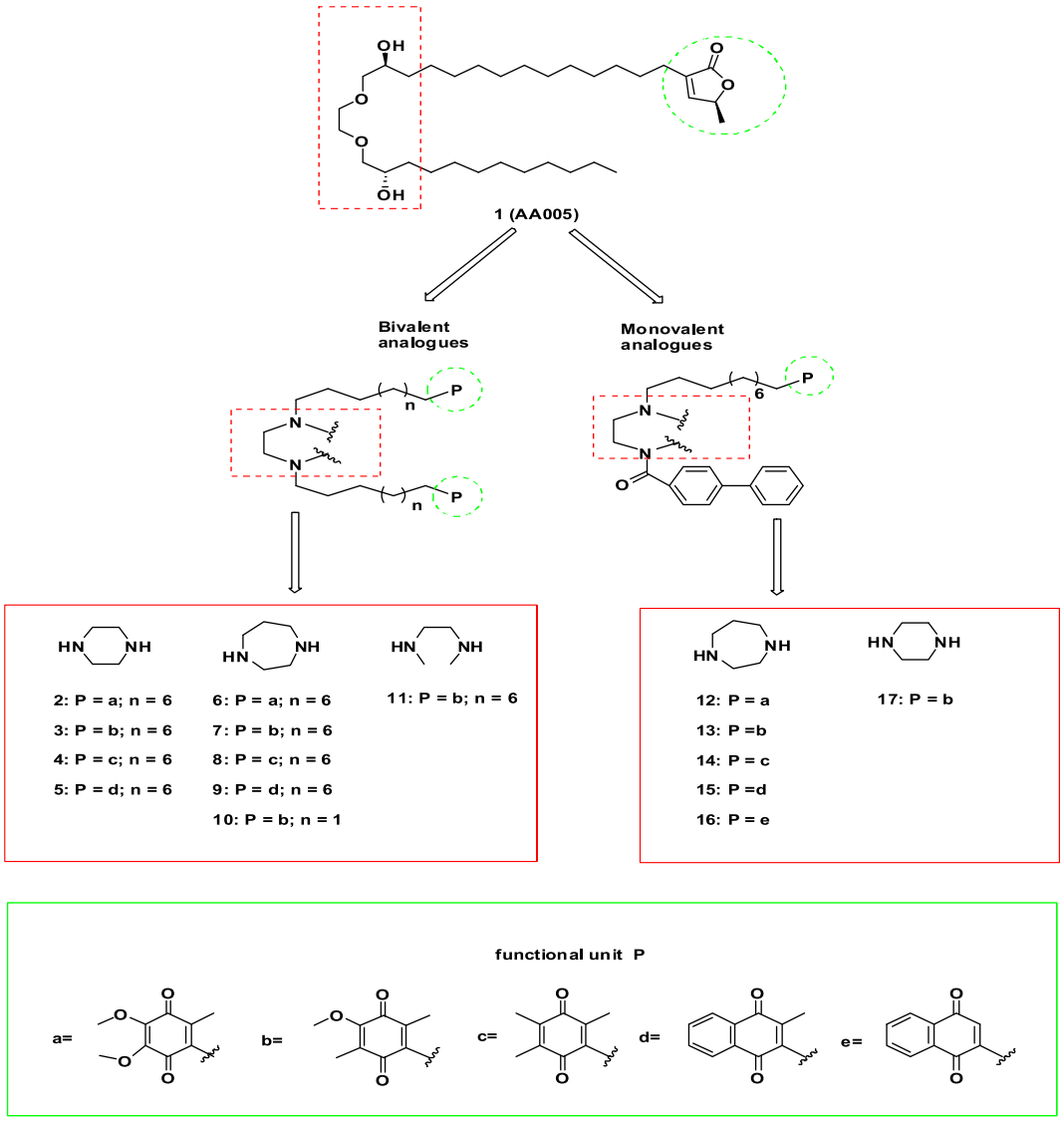

Figure 1. Design of new bivalent analogues of annonaceous acetogenins.

equivalent for the γ-lactone of natural acetogenins. Therefore, diverse analogues of ubiquinone were designed as an essential functionality for our bivalent mimicking. Hydrophilic piperazine ring was introduced in the middle because of its structural similarities with the bis-THF rings of natural acetogenins. We envisioned that modification of the conformational property of piperazine ring would affect inhibitory activity. Accordingly, a series of homopiperazine derivatives were also designed for comparison. The hydrophobic hydrocarbon chains of natural annonaceous acetogenins retain the amphiphilic nature of these acetogenin mimetics.

Syntheses of the ubiquinone analogues were shown in Scheme 1. Oxidation of 2,3,5-trimethylphenol **18** got **19** in 90% yield.[22] Treatment of 2,5-dimethyl-*p*-benzoquinone with acetic anhydride and boron trifluoride-etherate provided **21** in 92% yield. Then, compound **21** was treated with sodium hydroxide and dimethyl sulfate in methanol to afford **22** in 80% yield. Subsequent oxidation of compound **22** with phenyliodine diacetate (PIDA) provided **23** in 60% yield.[22] Finally, compounds **27**–**32** were synthesized in parallel via radical alkylation of the substituted quinones **19** and **23**–**26** in 20–56% yields,[23] via decarboxylation of the bromo-acid under silver nitrate and ammonium persulfate at 75 °C.

Syntheses of bivalent analogues **2**–**11** were shown in Scheme 2. Parallel treatment of piperazine or homopiperazine with corresponding quinones **27**–**32**, in the presence of catalytic amount of tetrabutylammonium iodide in acetonitrile under refluxing conditions, afforded the corresponding analogues **2**–**11**.

A number of monovalent analogues **12**–**17** were also synthesized (Scheme 3). Coupling of 4-biphenylcarboxylic acid with benzyl piperazine-1-carboxylate followed by hydrogenation of **37** afforded compound **39** in 60% yield. Compound **40** was prepared by the same procedure starting from benzyl 1,4-diazepane-1-carboxylate. Parallel reactions of compound **39** or **40** with quinones **27**–**31**, respectively, in the presence of catalytic amount of tetrabutylammonium iodide in acetonitrile under refluxing conditions, afforded monovalent analogues **12**–**17**.

All the synthesized compounds **1**–**17** were evaluated with MTT assays for their inhibitory activity against the proliferation of human gastric cancer cell line (SGC7901), colorectal carcinoma cell line (HCT-116), human lung fibroblasts (HLF) and human bronchial epithelial cell line (16HBE). The results are summarized in Table 1. Among the compounds **2**–**5** featuring a common piperazine ring in the middle region, compound **2** bearing natural ubiquinone ring at